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## The Heck reaction in the production of fine chemicals

Johannes G. de Vries

**Abstract.** An overview is given of the use of the Heck reaction for the production of fine chemicals. Five commercial products have been identified that are produced on a scale in excess of 1 ton/year. The herbicide Prosulfuron<sup>TM</sup> is produced via a Matsuda reaction of 2-sulfonatobenzenediazonium on 3,3,3-trifluoropropene. The sunscreen agent 2-ethylhexyl *p*-methoxy-cinnamate has been produced on pilot scale using Pd/C as catalyst. Naproxen<sup>TM</sup> is produced via the Heck reaction of 2-bromo-6-methoxy-naphthalene on ethylene, followed by carbonylation of the product. Monomers for coatings are produced via a Heck reaction on 2-bromo-benzocyclobutene. A key step in the production of the antiasthma agent Singulair<sup>TM</sup> is the use of the Heck reaction of methyl 2-iodo-benzoate on allylic alcohol (**18**) to give ketone (**20**). The high cost of palladium has spurred much research aimed at the development of more active palladium catalysts. Ligandless catalysts are very attractive for production, but work only on reactive substrates. Palladacycles are much more stable than Pd-phosphine complexes and can be used at higher temperatures. The same effect has been reached with pincer ligands. Bulky ligands lead to coordinatively unsaturated Pd-complexes, which are highly active for the Heck reaction. Recycle of palladium catalysts is also very important to reduce cost. Immobilization of catalysts by attaching ligands to solid support is not very useful, because of leaching and reduced activity. In ligandless Heck reactions the catalyst can be precipitated on carriers such as silica, dicalite, or celite. This material can be restored to its original activity by treatment with I<sub>2</sub> or Br<sub>2</sub>.

**Key words:** homogeneous catalysis, palladium, arylation, olefination, ligandless, catalyst recycle.

**Résumé :** On présente une revue de l'utilisation de la réaction de Heck dans la production de produits chimiques fins. On a identifié cinq produits commerciaux qui sont produits sur une échelle supérieure à une tonne par année. L'herbicide Prosulfuron<sup>®</sup> est produit par le biais d'une réaction de Matsuda du 2-sulfonatobenzènediazonium sur le 3,3,3-trifluoropropène. L'agent solaire 4-méthoxycinnamate de 2-éthylhexyle a été produit à l'échelle pilote à l'aide d'un catalyseur de Pd/C. Le Naproxen<sup>®</sup> est produit par le biais d'une réaction de Heck du 2-bromo-6-méthoxynaphtalène sur l'éthylène, suivie d'une carbonylation du produit. Des monomères de couches protectrices sont produits par le biais d'une réaction de Heck sur le 2-bromobenzocyclobutène. Une étape clé dans la production de l'agent antiasthmatisique Singulair<sup>®</sup> est l'utilisation de la réaction de Heck du 2-iodobenzoate de méthyle sur l'alcool allylique **18** pour obtenir la cétone **20**. Le prix élevé du palladium a provoqué beaucoup de recherches dans le but de développer des catalyseurs du palladium qui soient plus actifs. Les catalyseurs sans ligands sont très attrayants pour la production, mais ils ne sont utiles qu'avec des substrats réactifs. Les cycles palladiés sont beaucoup plus stables que les complexes Pd/phosphine et ils peuvent être utilisés à des températures plus élevées. On peut obtenir le même effet avec des ligands en forme de pinces. Les ligands encombrés conduisent à des complexes à coordination insaturée du Pd qui sont très actifs pour la réaction de Heck. Le recyclage des catalyseurs de palladium est important afin de minimiser les coûts. L'immobilisation des catalyseurs en attachant des ligands à un support solide n'est pas très utile en raison du lessivage et de la réduction de l'activité. Dans les réactions de Heck sans ligand, il est possible de précipiter le catalyseur sur des porteurs, comme la silice, la dicalite ou la célite; ce matériel peut être ramené à son activité originale par traitement avec du I<sub>2</sub> ou du Br<sub>2</sub>.

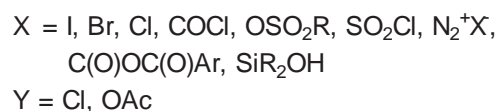
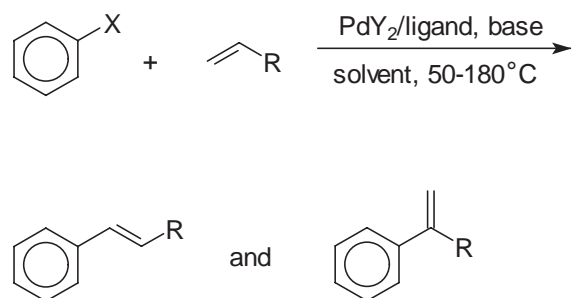
**Mots clés :** catalyse hétérogène, palladium, arylation, oléfination, sans ligand, recyclage du catalyseur.

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*Dedicated to Brian James, a great scientist and a superb lecturer with a keen sense of humour, on the occasion of his 65<sup>th</sup> birthday.*

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**Scheme 1.** The Heck reaction.

## Introduction

Fine chemicals are produced on a scale of roughly between 1 and 10 000 tons per year. They comprise pharmaceuticals, agrochemicals, polymer additives, flavours and fragrances, food and feed additives, and chemical intermediates to name the most important classes. With relatively few exceptions, fine chemicals are produced via stoichiometric chemistry as this is easily scaled up and does not need specialized equipment. Unfortunately, these production methods also lead to relatively large amounts of waste (1).

Use of homogeneous catalysis has a number of obvious advantages (1–3): (i) less waste; (ii) lower cost, in particular if shortcuts in total syntheses can be achieved; (iii) high chemo- and regioselectivity, easily tuned by the ligands; (iv) asymmetric catalysis for the single step production of enantiopure fine chemicals.

If a product grows to a large volume, use of catalysis in a second-generation process becomes attractive because low cost is essential. Prime examples are Ibuprofen<sup>TM</sup> (carbonylation) (5), Naproxen<sup>TM</sup> (Heck reaction and carbonylation) (6), malonate esters (carbonylation) (7), and Metolachlor<sup>TM</sup> (asymmetric hydrogenation) (8).

The lack of homogeneous catalysis in first generation processes is very apparent in the production of pharmaceuticals. This is related to the limited duration of patent protection inducing a very strong time-to-market incentive. Because of this it is not possible to drastically change complex synthesis routes. Fortunately, there is an increasing interest in the use of homogeneous catalysis among medicinal chemists.

The history of homogeneous catalysis fine chemicals was initially largely dominated by asymmetric catalysis, particularly enantioselective hydrogenations (9). Recently, palladium catalysed aromatic substitution reactions have been used increasingly for the production of fine chemicals. In the past few years, five new processes based on the use of the Heck reaction have been reported.

## The Heck reaction

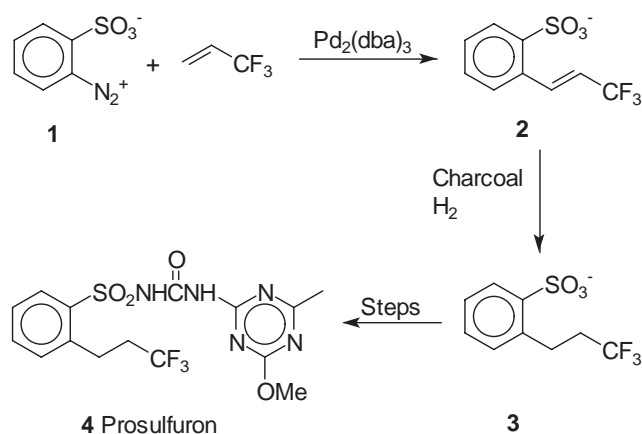
The Heck arylation reaction (Scheme 1), invented independently by Mizoroki and Heck (10) in 1970 establishes a bond between olefins and aromatic rings. Initially, reports only mentioned the use of aryl bromides and iodides as arylating agent. Later, variants were developed using aromatic triflates (11), aryl chlorides (12), aryl sulfonyl chlorides (13), aromatic diazonium salts (14) (the Matsuda reaction), aryl anhydrides (15), aryl chlorides (16–20), and arylsilanols (21). Consequently, the number of commercially available aromatic substrates is very high. The diazonium salts work at room temperature or below and thus are suitable for reactions with thermally labile olefins. In situ preparation of the diazonium salt from the aniline during the Heck reaction has also been reported (22). The variant using aromatic anhydrides only produces the aromatic acid as side product, which can be recycled. In addition it does not need phosphine ligands or a base (15). Hence, this reaction is salt free.

Most heteroaromatic halides and pseudohalides can be used in the Heck reaction, though sometimes substrates with halide *ortho*- to the heteroatom cause problems (10).

The Heck reaction works best with alkenes containing electron-withdrawing groups and in most cases gives the  $\beta$ -arylated products exclusively. Olefins with electron-donating groups give rise to mixtures of  $\alpha$ - and  $\beta$ -arylated products. If palladium complexes with bidentate ligands are used the regioselectivity can be determined by the choice of leaving groups. Noncoordinating anions like triflate lead mainly to the  $\alpha$ -arylated products, whereas halides predominantly give the  $\beta$ -products (10e). Simple olefins may suffer from Pd-catalyzed isomerization reactions leading to mixtures. Acetylenes may also be used and are generally more reactive than olefins (10).

Pd-catalysts are used with very few exceptions, usually  $\text{PdCl}_2$  or  $\text{Pd}(\text{OAc})_2$  alone or in combination with  $\text{Ph}_3\text{P}$  or *o*- $\text{ToI}_3\text{P}$  (2 or 3 equiv). Almost all Heck reactions require the presence of a base, which is often triethylamine. The combination  $\text{Pd}(\text{OAc})_2$ ,  $\text{MHCO}_3$  ( $M = \text{Na, K}$ ),  $\text{KOAc}$  or  $\text{K}_2\text{HPO}_4$  with a phase transfer salt is also often used (Jeffery conditions) (10f). The ligand, the counter ion, the base, the phase transfer salt, and the solvent all have a profound influence on the rate and the selectivity of the reaction; many of these effects are related to the oxidation state and the coordination chemistry of the catalyst (23). It is also possible to use heterogeneous palladium catalysts such as  $\text{Pd/C}$  (24). Palladium clusters have also shown to be active (25); in fact Pd-clusters seem to form in most phosphine free Heck reactions. There is an ongoing debate whether the clusters themselves are catalytically active or if it is a monomeric soluble form of Pd that is the active catalyst (10i, 26). Obviously, to increase activity it is of importance to keep the size of these nanoclusters small. This can be achieved by the addition of tetraalkylammonium salts (Jeffery conditions) (10f) or with weakly binding polymers (27) or dendrimers (28). In most cases the active species is based on Pd(0), though it can be anionic (23). Proposals have also been advanced for Pd(II)–Pd(IV) cycles (29–31).

Typical solvents for the Heck reaction are dipolar non-protic solvents like DMF and NMP. An asymmetric variant

**Scheme 2.** Synthetic scheme for the production of the herbicide Prosulfuron™.

of the Heck reaction has been developed (32). The scope of this transformation has been limited thus far.

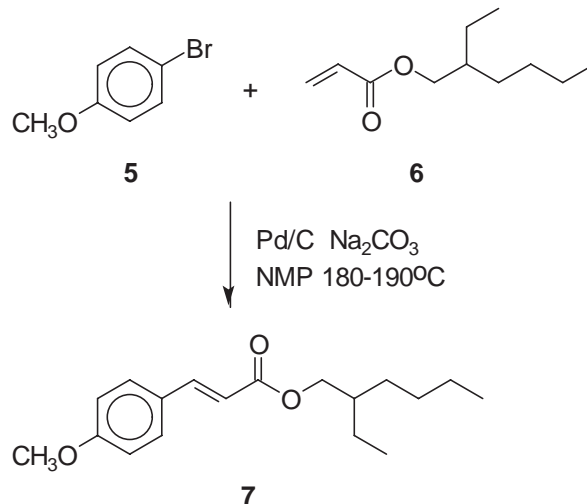
### Use of the Heck reaction for the production of fine chemical intermediates

#### The herbicide Prosulfuron™

The first reported example of industrial use of the Heck reaction was for the production of Prosulfuron™, a new and highly active herbicide, by Ciba-Geigy (now Novartis) (33). In this instance, the Matsuda variant was used to great advantage as the substrate also contains a sulfonate group. The 2-sulfonatobenzenediazonium, which was prepared by diazotization of the aniline, is a neutral compound and relatively stable. The Heck reaction of this betaine on 3,3,3-trifluoropropene was performed at 15°C in HOAc using Pd<sub>2</sub>(dba)<sub>3</sub> (0.5–1 mol%) as catalyst (Scheme 2). It was not necessary to isolate the Heck product. After addition of some active carbon to deposit the palladium on, the double bond was hydrogenated. Not only was the catalyst used in two consecutive steps, this method also allowed the catalyst to be reclaimed by filtration in 95% yield. The reaction is performed in a single reactor without isolation of the intermediates. The average yield per step is in excess of 90%.

#### Sunscreen agent via a ligandless Heck reaction

Companies producing bromine and aromatic bromides are of course in an excellent position to apply the Heck reaction. This advantage is not limited to the raw material position, but also involves the ability to recycle the bromide salts that are formed as waste. Because of the presence of large deposits of bromide, Israel has a flourishing organobromide industry. This has led to the development of a new process for the production of 2-ethylhexyl *p*-methoxy-cinnamate, the most common UV-B sunscreen (34). The process involves the Heck reaction of *p*-bromoanisole with 2-ethylhexyl acrylate (Scheme 3). In this process, palladium on carbon is used as the catalyst without any ligands. This has the disadvantage of relatively low reactivity as compared to most homogeneous catalysts, necessitating a reaction temperature of 190°C. Also, as a result of the high reaction temperature some diarylation is found, mainly the 3,3'-isomer in up to

**Scheme 3.** Sunscreen agent via the Heck reaction.

4%. Presumably, some palladium dissolves during the reaction, but after consumption of the starting materials all palladium precipitates, allowing easy catalyst recovery. The reaction mixture can contain up to 15% of water, which actually has an accelerating effect. This process, which was developed at the IMI institute for R & D in Israel, has been used on pilot scale to produce several tons of sunscreen agent in yields ranging from 75–92%.

#### Naproxen™ via Heck reaction and hydroxycarbonylation

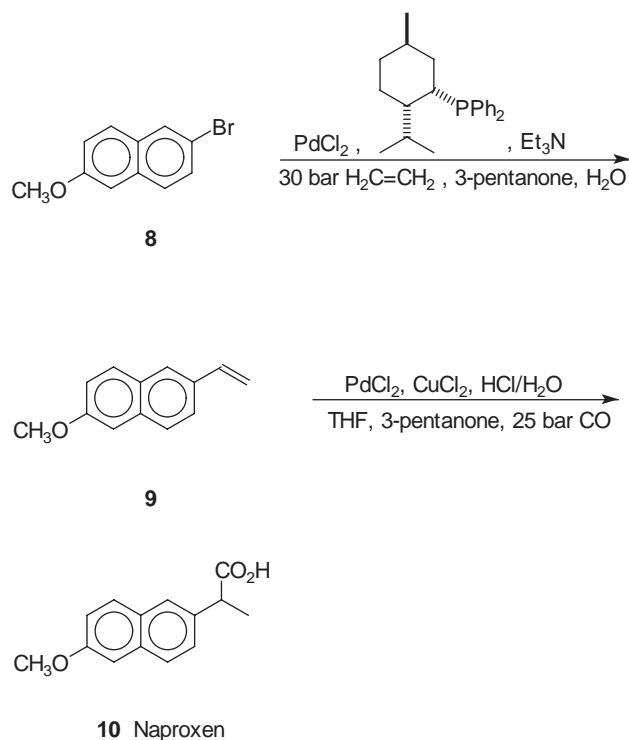
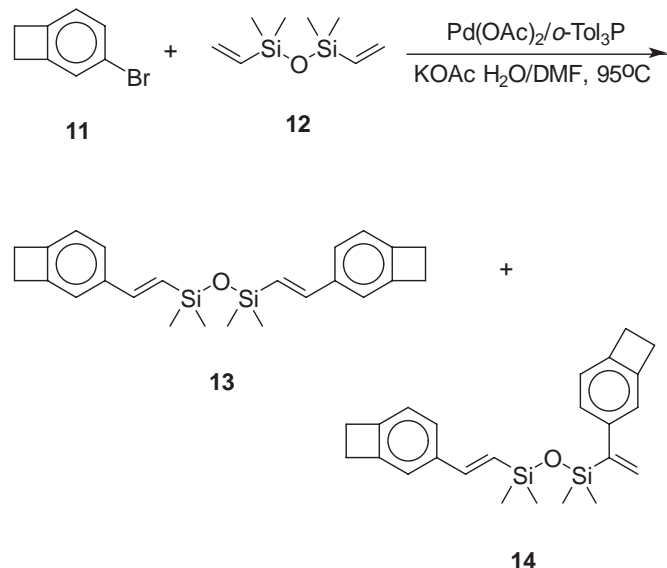
Another producer of organobromine compounds, Albemarle, developed a new process for the production of Naproxen™, based on the Heck reaction of 2-bromo-6-methoxynaphthalene with ethylene, followed by carbonylation to Naproxen™ (Scheme 4) (6, 35, 36). The bromide already was an intermediate for the existing production of Naproxen™ and hence was available at a low price (37).

The key to the commercial success was finding a catalyst for the Heck reaction that was sufficiently active. This was accomplished by screening ligands based on their steric and electronic properties. From these results it was found that a phosphine ligand with steric and electronic properties in the middle of those screened would be optimal. These properties were found in neomenthyldiphenylphosphine. Because of the high activity of the catalyst it was possible to use a substrate:catalyst ratio of between 2000 and 3000 with the reaction going to completion at 95–105°C within a few hours. An ethylene pressure of around 3 kPa was used. This process is run on a scale of 500 tons per year. The bromide is recycled.

The hydroxycarbonylation process is catalyzed by a mixture of PdCl<sub>2</sub>, CuCl<sub>2</sub> and HCl.

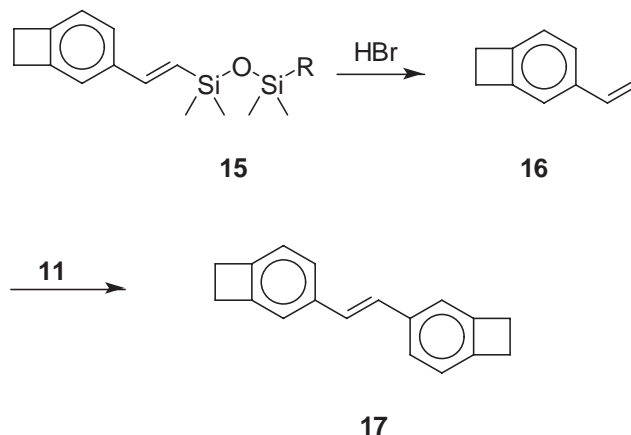
#### Monomers for coatings of electronic components

The mild conditions of the Heck reaction are also highly suitable for making carbon–carbon bonds with aromatic compounds that are thermally labile. This was the key to success in the production of benzocyclobutene-containing monomers. These are used to form coatings (known as

**Scheme 4.** Naproxen™ via Heck reaction and hydroxycarbonylation.**Scheme 5.** Monomers for coatings via the Heck reaction.

Cyclotene™ for electronic components. The benzocyclobutene groups form *ortho*-quinone-dimethanes upon heating to  $180^\circ\text{C}$ , which may react with the double bond introduced by the Heck reaction, thus leading to cross-linking by Diels–Alder reaction.

The monomers are formed by Heck reaction of 4-bromobenzocyclobutene with tetramethyldivinylsiloxane catalyzed by  $\text{Pd}(\text{OAc})_2/o\text{-Tol}_3\text{P}$  in  $\text{DMF}-\text{H}_2\text{O}$  using KOAc as base (Scheme 5) (38). The optimal catalyst for this reaction

**Scheme 6.** Mechanism of formation of the stilbene side product.

was found after screening a range of phosphorus ligands at  $95^\circ\text{C}$ . Tri-*ortho*-tolylphosphine gave the best results of the commercially available ligands in terms of product yield (83%). No correlation was found between ligand parameters on one hand, and conversion of bromide, yield of product, or regioselectivity on the other hand. The ligand parameters used were cone angle for bulkiness and  $\text{p}K_a$  for electronic properties.

A major side product (3–11%) in these reactions is the stilbene (17), which is formed by desilylation of the initially formed monoarylated disiloxane (15) followed by Heck reaction on the vinyl group (Scheme 6). Initial results using  $\text{Et}_3\text{N}$  as base gave much higher yields of this side product.

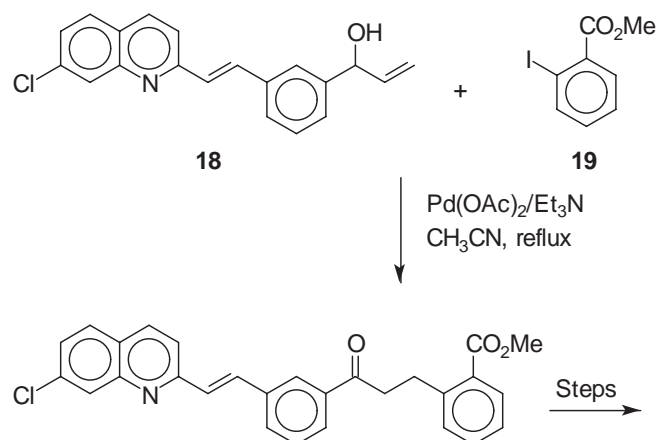
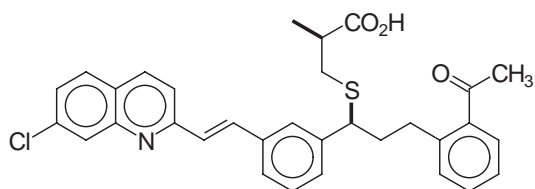
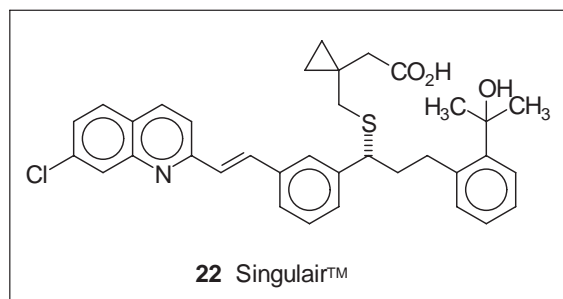
This Heck reaction is performed by Dow on a scale of several tons per year.

### The Heck reaction as the key step in the production of an antiasthma agent

An important aspect of the attractiveness of the Heck reaction is the ability to form carbon–carbon bonds without the use of strongly basic reagents such as Grignards and lithiated carbon nucleophiles. Hence, the functional group tolerance of the Heck reaction is very wide allowing its use in the latter stages of a total synthesis. This aspect is very important in the production of Merck's  $\text{LTD}_4$  antagonist Singular™ (22) (39) that has been introduced on the market as an antiasthma agent. A synthesis has been published for the closely related L-699 392 (21) (Scheme 7) (40). The key step in the synthesis is the Heck reaction of methyl 2-iodobenzoate with allylic alcohol (18). Because of the high reactivity of these substrates it was possible to use ligandless  $\text{Pd}(\text{OAc})_2$  as catalyst with  $\text{Et}_3\text{N}$  as base in  $\text{CH}_3\text{CN}$  as solvent. With 1 mol% of catalyst the reaction is complete in 1 h. A minor by-product was formed via arylation of the 2-position. However, the product could be obtained in pure form by crystallization.

In this variant, reaction on the allylic alcohol leads to the formation of a ketone, because  $\beta$ -hydride elimination of the palladium–alkyl intermediate leads to the preferential formation of the enol.

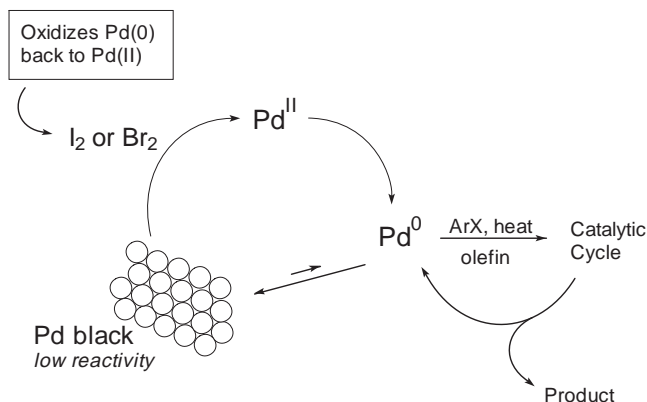


**Scheme 7.** The Heck reaction in the production of antiasthma agents.**20****21** L 699,392**22** Singularair™

## Development aspects

A major aspect in the development of a homogeneous catalyzed reaction is the cost of the catalyst. This in turn is strongly dependent on two important parameters: (i) The activity of the catalyst expressed as turnover frequency (TOF: mol of product/mol of catalyst h); (ii) The stability of the catalyst expressed as total turnover number (this might include recycling; TON = mol of product/mol of catalyst).

For this reason, much effort has been put into the development of new, more active, and more stable palladium catalysts. The palladacycle developed by Herrmann et al. (17) is a good example. Because of its increased stability, the catalyst can be used at higher temperatures, thus producing higher reaction rates. In addition, unreactive arylating agents like aryl chlorides can be used. More variations on this

**Scheme 8.** A practical catalyst recycle for ligandless Heck reactions.

theme are the use of bulky phosphite (18, 41) or phosphoramidite ligands (42), carbene ligands (43, 44), and pincer ligands (31, 45). Another interesting, cheap, and very active class of catalysts are the palladacycles based on aromatic compounds with side chains containing N (41, 46), O (47), or S (48, 49). The more active catalysts also have allowed the use of chloroarenes as arylating agents, which is tremendously important because of the much wider commercial availability and the lower costs of these compounds (16–20).

Separation of the product can sometimes be hampered by the presence of a phosphine ligand. Therefore, ligandless Heck reactions are preferred where possible, as shown in three of the above five cases.

Because of the steadily rising cost of palladium, catalyst recovery and recycle has become a major issue. Recovery is easy in the case of the ligandless Heck reactions as the catalyst precipitates completely once all the substrate has been used up. If ligands are used this can be a problem, though sometimes water-soluble ligands can be used to allow for two-phase catalysis (50–53). Ionic liquids have also been reported as an aid in catalyst recycle (54–56). The recovered catalyst is usually returned to the catalyst manufacturer for reclaiming as catalyst activity is greatly diminished. Recycling methods based on the immobilization of ligands are usually flawed, as the instability of the palladium complexes will invariably lead to leaching (10i). In addition, reactivity is usually severely compromised. Immobilization of ligandless palladium has some merit (57). Even though leaching occurs extensively, the palladium precipitates on the support at the end of the reaction. However, these catalysts are usually less active.

Recently, a new method for catalyst recycle was reported from our laboratories (58, 59). In this method,  $\text{Pd}(\text{OAc})_2$  is used as ligandless catalyst. At the end of the reaction, the catalyst precipitates in >99% as  $\text{Pd}(0)$  on an inexpensive carrier material like silica, dicalite, or celite. This catalyst is about 10 times less active than the  $\text{Pd}(\text{OAc})_2$  that is used initially. However, full catalytic activity can be restored by the addition of a few equivalents of  $\text{I}_2$  or  $\text{Br}_2$  (Scheme 8). These halogens oxidize Palladium(0) to  $\text{Pd}(\text{II})$  which is then reduced again during the next cycle to form highly active catalytic species.

## Conclusion

The Heck reaction is finding increasing use for the production of fine chemicals on a scale of 1–500 tons per year. At least five published cases are known of products that have been produced on a scale of more than 1 ton using the Heck reaction. Advantages when compared to more classical methods such as Friedel–Crafts chemistry are superb functional group tolerance, mild conditions, less waste, and sometimes a shorter route than the original stoichiometric route. This has spurred renewed activity in the area of development of new, faster and more stable catalysts. Catalyst recycle is particular easy with ligandless catalysts, where treatment of the precipitated Pd with I<sub>2</sub> leads to full regeneration of activity.

## Acknowledgements

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